Intensive Care Med
https://doi.org/10.1007/s00134-024-07647-6

EDITORIAL

Diagnostic tests for infections in critically ill immunocompromised patients

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An increasing number of critically ill patients are immunocompromised, posing unique diagnostic challenges for intensive care physicians. These patients have a heightened susceptibility to infections, with a significant survival impact of delayed or unknown diagnosis [1]. Immunocompromised patients form a highly heterogeneous population, where disease- or treatment-related immune deficiency significantly impacts the risk of specific pathogens [2]. For example, a T-cell deficit, as seen in patients with human immunodeficiency virus (HIV) infection or patients receiving calcineurin inhibitors, predisposes patients to infections with fungi such as *Pneumocystis jirovecii*, Aspergillus, and Cryptococcus, as well as herpes viruses. Patients with impaired humoral immunity (such as in cases of asplenia, and hypogammaglobulinemia) are at higher risk for severe infections caused by encapsulated bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenza.* Short-term (<7 days) chemotherapy-induced neutropenia predisposes patients to bacterial translocation with gram-negative bacteria or intravascular device bacterial infection, while prolonged neutropenia raises the risk for fungal infection.

Moreoever, differentiating infections from non-infectious organ failure in immunocompromised patients, such as tumor lysis syndrome, drug toxicity (e.g., cytarabine toxicity during acute leukemia), or hemophagocytic lymphohistiocytosis, is particularly challenging. These differential diagnoses are made difficult in immunocompromised intensive care unit (ICU) patients. For instance, hyperferritinemia and hemophagocytosis can occur in the context of septic shock and are not specific to hemophagocytic lymphohistiocytosis [3].

Diagnostic strategy

An effective diagnostic approach requires integrating multimodal information, including the type of immune deficit, clinical and radiologic presentations, pathogen-focused techniques, and biomarkers of host response. Clinical and radiologic evaluations are the cornerstone of assessing sepsis and identifying its source. In the context of acute respiratory failure, the mnemonic DIRECT has been proposed for rapid diagnostic evaluation based on the number of Days since respiratory symptom onset, type of Immunodeficiency, Radiographic pattern, clinician Experience, Clinical findings, and high-resolution computed Tomography findings [4]. After having identified the type of immunodeficiency, the clinical and radiologic evaluation and the suspected site of infection will guide the selection of pathogens to be investigated (Fig. 1). This approach allows for non-invasive diagnosis and limits the use of bronchoalveolar lavage (BAL), where clinicians should carefully assess the benefit-risk ratio.

Gaps in diagnosing infection in immunocompromised patients

Clinical manifestations or microbiological documentation in immunocompromised patients may be affected by underlying immune defects, antimicrobial prophylaxis, or responsible pathogens. For example, neutropenia alters the white-cell count in cerebrospinal fluid (CSF), making the diagnosis of meningitis more challenging [5]. Additionally, the diagnostic value of sepsis biomarkers can be decreased: steroids, anti-interleukin (IL)-6/IL-1 therapies reduce C-reactive protein levels, and although procalcitonin levels are rarely affected by malignancy (thyroid cancer, small cell lung cancer) or drugs (T-cell-directed

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therapies), its utility is very limited in immunocompromised patients for guiding antimicrobial therapy or determining the type of pathogen involved[6]. In addition, due to the frequent use of broad-spectrum antibiotics at the time of sample collection, gram staining and culturing might have lower than usual sensitivity, resulting in a lower rate of documented infections. Moreover, impaired humoral immunity and cross-reactions (from intravenous immunoglobulins or plasmapheresis), limit the value of serological assays in this context [7]. Diagnostic tests have been developed, allowing the detection of urine (e.g., Pneumococcus or Legionella) or serum antigens (eg, galactomannan, β-D-glucan, or Cryptococcus) [8]. Despite their undeniable value, several factors affect their performance, such as sample type (higher usefulness of galactomannan in BAL than in serum or CSF, the responsible pathogen (higher sensitivity of galactomannan for non-fumigatus Aspergillus species) [9], host factors [10](e.g., underlying diseases, antifungal prophylaxis, neutropenia (serum galactomannan is more sensitive in neutropenic patients with angioinvasive aspergillus, but less effective in non-neutropenic patient)), or cross-reactions (false positives for β-D-glucan or galactomannan due to intravenous immunoglobulins, therapeutic antibodies, or antibiotics) [11, 12]. Molecular diagnostic methods like polymerase chain raction (PCR) are promising tools. These methods can be pathogen-specific Cytomegalovirus, Toxoplasma, Pneumocystis, Aspergillus or capable of detecting multiple targets (respiratory, meningitis–encephalitis, gastrointestinal panels). Recently, real-time PCRs working directly from whole blood have been developed. These tools increase the documentation rate and shorten identification time although they have certain limitations: they require predefined targets that may not match with prevalent pathogens (such as Nocardia, Stenotrophomonas, Cryptococcus…), their sensitivity varies depending on the sample location (e.g., BAL > nasal swab/CSF), and they usually do not provide precise information on antibiotic susceptibility, although antimicrobial resistance genes are increasingly available in new panels. Moreover, establishing causality between an identified pathogen and its involvement in the clinical presentation is sometimes hazardous (eg. detecting a respiratory virus in a nasal swab and diagnosing pneumonia), and there is a need for a consensus on defining thresholds to distinguish between colonization and infection, as seen in *Pneumocystis pneumonia* [13].

Metagenomic next-generation sequencing: advances and challenges

Metagenomic next-generation sequencing (mNGS) emerges as a promising diagnostic tool for identifying pathogens in immunocompromised patients, particularly when conventional methods falter. Plasma NGS has also

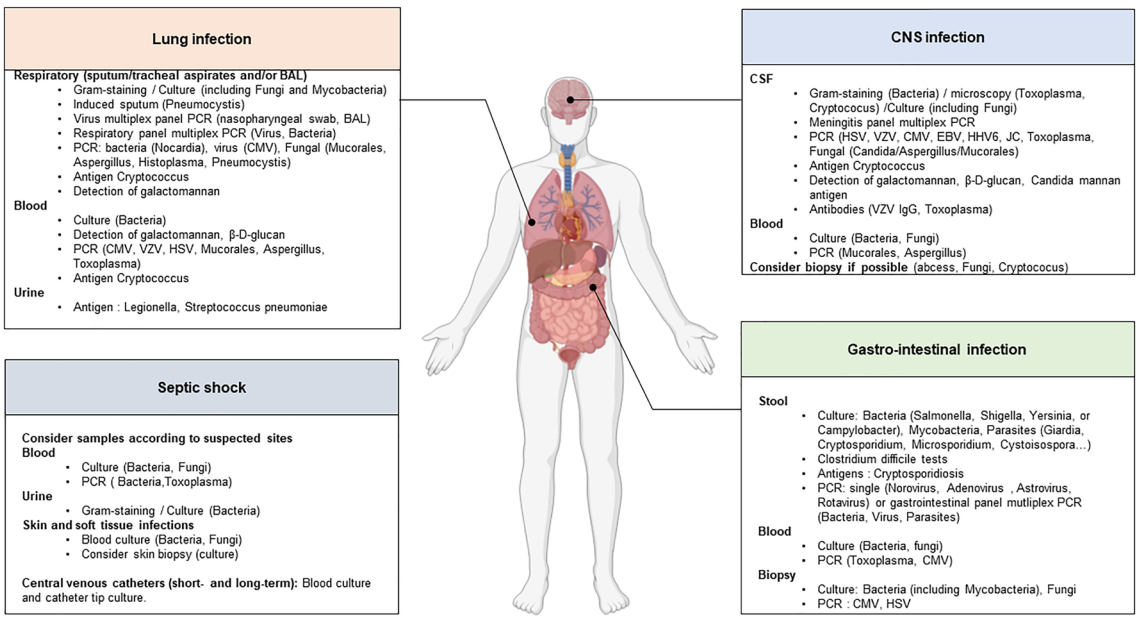
Lung infection
Respiratory (sputum/tracheal aspirates and/or BAL)
Gram-staining / Culture (including Fungi and Mycobacteria)
Induced sputum (Pneumocystis)
Virus multiplex panel PCR (nasopharyngeal swab, BAL)
Respiratory panel multiplex PCR (Virus, Bacteria)
PCR: bacteria (Nocardia), virus (CMV), Fungal (Mucorales, Aspergillus, Histoplasma, Pneumocystis)
Antigen Cryptococcus
Detection of galactomannan
Blood
Culture (Bacteria)
Detection of galactomannan, β-D-glucan
PCR (CMV, VZV, HSV, Mucorales, Aspergillus, Toxoplasma)
Antigen Cryptococcus
Urine
Antigen : Legionella, Streptococcus pneumoniae
CNS infection
CSF
Gram-staining (Bacteria) / microscopy (Toxoplasma, Cryptococus) /Culture (including Fungi)
Meningitis panel multiplex PCR
PCR (HSV, VZV, CMV, EBV, HHV6, JC, Toxoplasma, Fungal (Candida/Aspergillus/Mucorales)
Antigen Cryptococcus
Detection of galactomannan, β-D-glucan, Candida mannan antigen
Antibodies (VZV IgG, Toxoplasma)
Blood
Culture (Bacteria, Fungi)
PCR (Mucorales, Aspergillus)
Consider biopsy if possible (abcess, Fungi, Cryptococus)
Septic shock
Consider samples according to suspected sites
Blood
Culture (Bacteria, Fungi)
PCR (Bacteria,Toxoplasma)
Urine
Gram-staining / Culture (Bacteria)
Skin and soft tissue infections
Blood culture (Bacteria, Fungi)
Consider skin biopsy (culture)
Central venous catheters (short- and long-term): Blood culture and catheter tip culture.
Gastro-intestinal infection
Stool
Culture: Bacteria (Salmonella, Shigella, Yersinia, or Campylobacter), Mycobacteria, Parasites (Giardia, Cryptosporidium, Microsporidium, Cystoisospora…)
Clostridium difficile tests
Antigens : Cryptosporidiosis
PCR: single (Norovirus, Adenovirus , Astrovirus, Rotavirus) or gastrointestinal panel mutliplex PCR (Bacteria, Virus, Parasites)
Blood
Culture (Bacteria, fungi)
PCR (Toxoplasma, CMV)
Biopsy
Culture: Bacteria (including Mycobacteria), Fungi
PCR : CMV, HSV

Fig. 1 Proposed diagnostic tools according to suspected infection site. Please note that the sample location and suspected pathogens depend on clinical manifestations, underlying immune defects, and previously used prophylaxis. The diagnostic strategy should take into account such factors. Multiplex panel PCR targets may vary across manufacturers. *BAL* bronchoalveolar lavage, *CMV* cytomegalovirus, *EBV* Epstein Barr virus, *HHV6* human herpes virus 6, *IgG* immunoglobulin, *JC virus* John Cunningham virus, *PCR* polymerase chain reaction amplification, *HSV* herpes simplex virus, *VZV* varicella-zoster virus

proven useful in challenging diagnoses in immunocompromised patients. Studies investigating its application in plasma reveal a significant impact on clinical decision-making, highlighting its potential as a non-invasive "liquid biopsy" alternative [14]. Indeed, by analyzing blood samples, mNGS offers a streamlined approach to diagnosing infections, sparing patients from invasive procedures. Its utility extends to the diagnosis of fungal infections across pulmonary and extrapulmonary sites [15], although concerns persist regarding its sensitivity in distinguishing colonization from infection. In the context of neutropenic fever, where a pathogen is identified in only 30% of cases, mNGS shows promise in guiding early antimicrobial optimization, potentially revolutionizing management strategies in this challenging condition. Despite its potential, challenges persist, including turnaround time and clinical interpretation, which may limit its widespread adoption. Nonetheless, ongoing clinical trials seek to elucidate its role further, focusing on its performance and cost-effectiveness in specific clinical contexts.

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Declarations

Conflicts of interest
LZ reports receiving fees for lectures for MSD and Sanofi. AJ and GD declare no conflict of interest.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 24 July 2024 Accepted: 2 September 2024
Published online: 19 September 2024

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